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II. REMARKS

A. Status of the Claims

Claims 1, 4-20 and 28-30 are currently pending. Claims 21-24, 25-37 and 31-42 were previously cancelled. Claims 2 and 3 have been cancelled herein without prejudice. Claims 1, 11-20 and 28-30 have been amended without prejudice. Support for the amendments can be found in the application as originally filed, e.g. in the claims. It is respectfully submitted that no new matter has been added by virtue of this amendment.

B. Claim Rejections Under 35 U.S.C. § 103

In the Office Action, claims 1-20, and 28-30 were rejected under 35 U.S.C. §103(a) "as being unpatentable over the combined disclosures of Whitcomb (USPN 6,011,049 hereafter '049) and Byrd et al (USPN 6,191,162 hereafter '162)".

Applicants respectfully submit that the '049 patent in view of the '162 patent, fails to teach or suggest a controlled release oral dosage form which provides a mean time to maximum plasma concentration (T_{max}) of an antihyperglycemic drug from 5.5 to 7.5 hours after administration following dinner, as recited in the present claims.

Applicants respectfully disagree with the Examiner's position that the compositions of the '049 patent inherently possess the recited properties directed to a T_{max} of from 5.5 to 75 hours. The '049 patent provides a general description of ingredients for dosage forms of their purported invention at column 5, lines 26-34, but does not provide any parameters with respect to the optimization of the general description with respect to particular active agents such as metformin.

In fact, the only particular guidance with respect to metformin formulations suitable for the purported invention of the '049 patent is at column 4, lines 60-61, which states that

metformin “is available in tablets which contain 500 mg and 850 mg of active agent. These can be given up to two times a day or more.” Applicants submit that one skilled in the art would recognize that the inventors of the ‘049 patent are referring to Glucophage® as being suitable for use in their purported invention. Applicants submit herewith Exhibit A, a copy of The Physicians' Desk Reference (PDR), 1998 Edition, pages 795-800, which recites the description of Glucophage, the commercially available formulation for metformin hydrochloride.

The Examiner's attention is directed to page 797, Table 4 of PDR (Exhibit A) which sets forth that the Tmax provided by Glucophage® tablets is from 1.79 to 4.01 hours after administration. Applicants respectfully submit that the lower limit of the claimed Tmax range (i.e. 5.5 hours) is more than 25% of the highest Tmax value (i.e. 4.01 hours) provided by the only specific metformin formulation described in the ‘049 patent.

Therefore, Applicants respectfully submit that the information in Table 4 of the PDR is evidence that the metformin formulations of the ‘049 patent cannot be considered to inherently possess the claimed Tmax of 5.5 to 7.5 hours, as the only specific metformin formulation in the ‘049 patent provides different Tmax values.

The Examiner relies on the ‘162 patent as teaching “a controlled release formulation capable of reducing serum glucose levels.” However, the controlled release formulations described in the ‘162 patent are with respect to lipoic acid. With respect to metformin, the ‘162 patent states at column 8, line 42 that “it is preferable to administer metformin (particularly metformin hydrochloride tablets sold as Glucophage®) with controlled release lipoic acid formulations of the present invention.

Therefore, as discussed with respect to the ‘049 patent, Applicants respectfully submit that page 797, Table 4 of PDR (Exhibit A) is evidence that the metformin formulations of the ‘062 patent cannot be considered to inherently possess the claimed Tmax of 5.5 to 7.5 hours, as the only specific metformin formulation in the ‘062 patent provides different Tmax values.

Accordingly, Applicants respectfully submit that the present claims are not obvious over the '049 patent in view of the '162 patent and request that the rejection under 35 U.S.C. § 103(a) be removed.

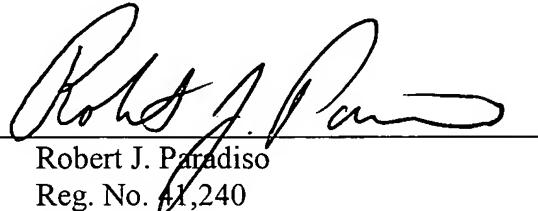
III. CONCLUSION

It is respectfully submitted that in view of the arguments presented, this case is now in condition for allowance. An early and favorable action on the merits is earnestly solicited.

According to currently recommended Patent Office policy, the Examiner is specifically authorized to contact the undersigned in the event that a telephonic interview will advance the prosecution of this application.

Respectfully submitted,
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By:


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DAILY DOSAGE OF DURICEF® SUSPENSION

Child's Weight		125 mg/5 mL	250 mg/5 mL	500 mg/5 mL
lbs	kg			
10		4.5	1 tsp	
20		9.1	2 tsp	1 tsp
30		13.6	3 tsp	1½ tsp
40		18.2	4 tsp	2 tsp
50		22.7	5 tsp	2½ tsp
60		27.3	6 tsp	3 tsp
70 & above.		31.8+	—	—

Reconstitution Directions for Oral Suspension

Bottle Size	Reconstitution Directions
100 mL	Suspend in a total of 67 mL water. Method: Tap bottle lightly to loosen powder. Add 67 mL of water in two portions. Shake well after each addition.
75 mL	Suspend in a total of 51 mL water. Method: Tap bottle lightly to loosen powder. Add 51 mL of water in two portions. Shake well after each addition.
50 mL	Suspend in a total of 34 mL water. Method: Tap bottle lightly to loosen powder. Add 34 mL of water in two portions. Shake well after each addition.

After reconstitution, store in refrigerator. Shake well before using. Keep container tightly closed. Discard unused portion after 14 days.

skin structure infections, the recommended daily dosage is 30 mg/kg/day in equally divided doses every 12 hours. In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosage of DURICEF® should be administered for at least 10 days.

See chart for total daily dosage for children.

[See first table above]

In patients with renal impairment, the dosage of cefadroxil monohydrate should be adjusted according to creatinine clearance rates to prevent drug accumulation. The following schedule is suggested. In adults, the initial dose is 1000 mg of DURICEF (cefadroxil monohydrate, USP) and the maintenance dose (based on the creatinine clearance rate [mL/min/1.73 M²]) is 500 mg at the time intervals listed below.

U.S. Patent Nos. 4,160,863
4,504,657

REFERENCES

- National Committee for Clinical Laboratory Standards, Approved Standard, *Performance Standards for Antimicrobial Disk Susceptibility Test*, 4th Edition, Vol. 10 (7): M2-A4, Villanova, PA, April, 1990.
- National Committee for Clinical Laboratory Standards, Approved Standard: *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 2nd Edition, Vol. 10 (8): M7-A2, Villanova, PA, April, 1990.

0783DIM-05

Revised February 1997
E3-B001-2.97

Shown in Product Identification Guide, page 307

Creatinine Clearances	Dosage Interval
0-10 mL/min	36 hours
10-25 mL/min	24 hours
25-50 mL/min	12 hours

Patients with creatinine clearance rates over 50 mL/min may be treated as if they were patients having normal renal function.

[See second table above]

HOW SUPPLIED

DURICEF® (cefadroxil monohydrate, USP) 500 mg Capsules: opaque, maroon and white hard gelatin capsules, imprinted with "PPP" and "784" on one end and with "DURICEF" and "500 mg" on the other end. Capsules are supplied as follows:

NDC 0087-0784-07	Bottle of 20
NDC 0087-0784-46	Bottle of 50
NDC 0087-0784-42	Bottle of 100
NDC 0087-0784-44	10 strips of 10 individually labeled blisters with 1 capsule per blister

Store at controlled room temperature (15°-30°C). DURICEF® (cefadroxil monohydrate, USP) 1 gram Tablets: white to off white, top bisected, oval shaped, imprinted with "PPP" on one side of the bisect and "785" on the other side of the bisect. Tablets are supplied as follows:

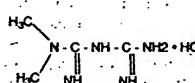
NDC 0087-0785-43	Bottle of 50
NDC 0087-0785-42	Bottle of 100
NDC 0087-0785-44	10 strips of 10 individually labeled blisters with 1 tablet per blister
NDC 0087-0785-45	4 packs of 10 individually labeled blisters with 1 tablet per blister

Store at controlled room temperature (15°-30°C). DURICEF® for Oral Suspension is orange-pineapple flavored, and is supplied as follows:

125 mg/5 mL	NDC 0087-0786-42	50 mL Bottle
	NDC 0087-0786-41	100 mL Bottle
250 mg/5 mL	NDC 0087-0782-42	50 mL Bottle
	NDC 0087-0782-41	100 mL Bottle

500 mg/5 mL	NDC 0087-0783-42	50 mL Bottle
	NDC 0087-0783-05	75 mL Bottle
	NDC 0087-0783-41	100 mL Bottle

Prior to reconstitution: Store at controlled room temperature (15°-30°C).



Metformin hydrochloride is a white to off-white crystalline compound with a molecular formula of $\text{C}_8\text{H}_{11}\text{N}_5 \cdot \text{HCl}$ and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether or chloroform. The pK_a of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

GLUCOPHAGE tablets contain 500 mg and 850 mg of metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: povidone, magnesium stearate and hydroxypropyl methylcellulose (hypromellose) coating.

CLINICAL PHARMACOLOGY

Antidiabetic Activity

GLUCOPHAGE is an antihyperglycemic agent which improves glucose tolerance in NIDDM subjects, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from those of sulfonylureas. GLUCOPHAGE decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity (increases peripheral glucose uptake and utilization). Unlike sulfonylureas, GLUCOPHAGE does not

Continued on next page

lucophage—Cont.

duce hypoglycemia in either diabetic or nondiabetic subjects (except in special circumstances, see PRECAUTIONS). It does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

a double-blind, placebo-controlled, multicenter U.S. clinical trial involving obese NIDDM patients whose hyperglycemia was not adequately controlled with dietary management alone (baseline fasting plasma glucose [FPG] of approximately 240 mg/dL), treatment with GLUCOPHAGE (to 2.55 g/day) for 29 weeks resulted in significant mean reduction in fasting and postprandial plasma glucose (FPG and HbA_{1c} of 59 mg/dL, 83 mg/dL, and 1.8%, respectively, compared to placebo group (see Table 1).

Table 1. GLUCOPHAGE vs Placebo Summary of Mean Changes from Baseline* in Plasma Glucose

HbA_{1c} and Body Weight, at Final Visit (29-week study)

	GLUCOPHAGE (n=141)	Placebo (n=145)	P-Value
G (mg/dL)			
Baseline	241.5	237.7	NS
Change at FINAL VISIT	-53.0	6.3	0.001 **
Hemoglobin A _{1c} (%)			
Baseline	8.4	8.2	NS
Change at FINAL VISIT	-1.4	0.4	0.001 **
Body Weight (lbs)			
Baseline	201.0	206.0	NS
Change at FINAL VISIT	-1.4	-2.4	NS

All patients on diet therapy at Baseline. Statistically significant.

monotherapy with GLUCOPHAGE may be effective in patients who have not responded to sulfonylureas or who have only a partial response to sulfonylureas or who have ceased to respond to sulfonylureas. In such patients, if adequate glycemic control is not attained with GLUCOPHAGE monotherapy, the combination of GLUCOPHAGE and a sulfonylurea may have a synergistic effect, since both agents act to improve glucose tolerance by different but complimentary mechanisms.

29-week, double-blind, placebo-controlled study of GLUCOPHAGE and glyburide, alone and in combination, was conducted in obese NIDDM patients who had failed to achieve adequate glycemic control while on maximum doses of glyburide (baseline FPG of approximately 250 mg/dL) (see Table 2). Patients randomized to continue on glyburide experienced worsening of glycemic control, with mean increases in FPG, PPG and HbA_{1c} of 14 mg/dL, 3 mg/dL and 2%, respectively. In contrast, those randomized to GLUCOPHAGE (metformin hydrochloride tablets) (up to 2.5 g/day) did not experience a deterioration in glycemic control, but rather a slight improvement, with mean reductions in FPG, PPG and HbA_{1c} of 1 mg/dL, 6 mg/dL and 0.4%, respectively. The combination of GLUCOPHAGE and glyburide was synergistic in reducing FPG, PPG and HbA_{1c} levels by 63 mg/dL, 65 mg/dL, and 1.7%, respectively. Compared to the results of glyburide treatment alone, the net differences with combined treatment were -77 mg/dL, -68 mg/dL and -1.9%, respectively (see Table 2). See table above.

The magnitude of the decline in fasting blood glucose concentration following the institution of GLUCOPHAGE (metformin hydrochloride tablets) therapy is proportional to the level of fasting hyperglycemia. Non-insulin-dependent diabetics with higher fasting glucose concentrations will experience greater declines in plasma glucose and glycosylated hemoglobin.

GLUCOPHAGE has a modest favorable effect on serum lipids, which are often abnormal in NIDDM patients. In clinical studies, particularly when baseline levels were abnormally elevated, GLUCOPHAGE, alone or in combination with a sulfonylurea, lowered mean fasting serum triglycerides, total cholesterol and LDL cholesterol levels and had no adverse effects on other lipid levels (see Table 3). See table above.

In contrast to sulfonylureas, body weight of individuals on GLUCOPHAGE tends to remain stable or may even decrease somewhat (see Table 1 and 2). In summary, metformin-treated patients showed significant improvement in all parameters of glycemic control (FPG; PPG and HbA_{1c}), stabilization or decrease in body weight, and a tendency to improvement in the lipid profile, particularly when baseline values are abnormally elevated.

Pharmacokinetics**Absorption and Bioavailability:**

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approxi-

Table 2. Combined GLUCOPHAGE/Glyburide (Comb) vs Glyburide (Glyb) or Glucophage (GLU) Monotherapy: Summary of Mean Changes from Baseline* in Plasma Glucose, HbA_{1c}, and Body Weight, at Final Visit (29-week study)

	Comb (n=213)	Glyb (n=209)	GLU (n=210)	Glyb vs Comb	GLU vs Comb	P-values
Fasting Plasma Glucose (mg/dL)						
Baseline	250.5	247.5	253.9	NS	NS	NS
Change at FINAL VISIT	-63.5	13.7	-0.9	0.001 **	0.001 **	0.02
Hemoglobin A _{1c} (%)						
Baseline	8.8	8.5	8.9	NS	NS	0.001
Change at FINAL VISIT	-1.7	0.2	-0.4	0.001 **	0.001 **	0.001
Body Weight (lbs)						
Baseline	202.2	203.0	204.0	NS	NS	NS
Change at FINAL VISIT	0.9	-0.7	-8.4	0.011 **	0.001 **	0.01

* All patients of glyburide, 20 mg/day, at Baseline

** Statistically significant

Table 3. Summary of Mean Percent Reduction of Major Serum Lipid Variables at Final Visit (29-week study)

	Glucophage vs. Placebo (% Change from Baseline)		Combined Glucophage/Glyburide vs. Monotherapy (% Change from Baseline)		
	Glucophage (n=141)	Placebo (n=145)	Glucophage (n=210)	Glyburide (n=213)	Glyburide (n=209)
Total Cholesterol	-5%*	1%	-2%	-4%**	
Total Triglycerides	-16%	1%	3%**	8%**	
LDL-Cholesterol	-8%*	1%	-4%**	6%**	
HDL-Cholesterol	2%	-1%	5%	3%	

* <0.05 vs. Placebo

** <0.05 vs. Glyburide

mately 50–60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration and 25% lower AUC in plasma and a 35 minute prolongation of time to peak plasma concentration following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution:

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins in contrast to sulfonylureas which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of GLUCOPHAGE (metformin hydrochloride tablets), steady state plasma concentrations of metformin are reached within 24–48 hours and are generally <1 µg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 µg/mL, even at maximum doses.

Metabolism and Elimination:

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see Table 4) is approximately 3.5 times greater than creatinine clearance which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations:**NIDDM Subjects:**

In the presence of normal renal function, there are no differences between single- or multiple dose pharmacokinetics

of metformin between diabetics and nondiabetics (see Table 4); nor is there any accumulation of metformin in the diabetic group at usual clinical doses.

Renal Insufficiency:

In subjects with decreased renal function (based on measured creatinine clearance), the plasma half-life of metformin is prolonged and the renal clearance decreased in proportion to the decrease in creatinine clearance (see Table 4).

Hepatic Insufficiency:

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency.

Geriatrics:

Limited data from controlled pharmacokinetic studies in healthy elderly subjects (age 65–85 years) show that plasma clearance is decreased, the half-life ($t_{1/2}$) is increased, compared to healthy young adults. From these data, it appears that the pharmacokinetics with aging is primarily a change in renal function (see Table 4). (See table at top of next page.)

Pediatrics:

No pharmacokinetic studies have been conducted in pediatric subjects.

Gender:

Metformin pharmacokinetic parameters are not significantly different in diabetic and nondiabetic women compared according to gender (males = 19, females = 19). Similarly, in controlled clinical studies comparing the antihyperglycemic effect of GLUCOPHAGE (metformin hydrochloride tablets) with glyburide, the effect was comparable in males.

Race:

No studies of metformin pharmacokinetics according to race have been performed. In controlled clinical studies of GLUCOPHAGE in patients with NIDDM, the antihyperglycemic effect was comparable in blacks (n=51) and hispanics (n=24).

INDICATIONS AND USE:

GLUCOPHAGE (metformin hydrochloride) monotherapy, is indicated as an adjunct to diet and exercise to improve blood glucose in patients with NIDDM. Metformin cannot be satisfactorily managed

INFORMATION

S' DESK REFER

Glyb)
laseline*
study)P-values
GLU vs
Comb

NS

J01 **

Glucophage—Cont.

Impaired hepatic function—Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOPHAGE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B₁₂ levels—A decrease to subnormal levels of previously normal serum vitamin B₁₂ levels, without clinical manifestations, is observed in approximately 7% of patients receiving GLUCOPHAGE in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B₁₂ absorption from the B₁₂-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of GLUCOPHAGE (metformin-hydrochloride tablets) or vitamin B₁₂ supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on GLUCOPHAGE and any apparent abnormalities should be appropriately investigated and managed (see Laboratory Tests).

Certain individuals (those with inadequate vitamin B₁₂ or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B₁₂ levels. In these patients, routine serum vitamin B₁₂ measurements at two- to three-year intervals may be useful.

Change in clinical status of previously controlled diabetic—A diabetic patient previously well controlled on GLUCOPHAGE who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, GLUCOPHAGE must be stopped immediately and other appropriate corrective measures initiated (see also WARNINGS).

Hypoglycemia—Hypoglycemia does not occur in patients receiving GLUCOPHAGE alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas) or ethanol.

Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose—When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold GLUCOPHAGE and temporarily administer insulin. GLUCOPHAGE may be reinstated after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with GLUCOPHAGE or sulfonylurea monotherapy, combined therapy with GLUCOPHAGE (metformin hydrochloride tablets) and sulfonylurea may result in a response. Should secondary failure occur with combined GLUCOPHAGE/sulfonylurea therapy, it may be necessary to initiate insulin therapy.

Information for Patients:

Patients should be informed of the potential risks and advantages of GLUCOPHAGE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the WARNINGS and PRECAUTIONS sections should be explained to patients. Patients should be advised to discontinue GLUCOPHAGE immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOPHAGE, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counselled against excessive alcohol intake, either acute or chronic, while receiving GLUCOPHAGE.

GLUCOPHAGE alone does not usually cause hypoglycemia, although it may occur when GLUCOPHAGE is used in conjunction with oral sulfonylureas. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients.

(See Patient Labeling Printed Below).

Laboratory Tests:

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also DOSAGE AND ADMINISTRATION).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with GLUCOPHAGE (metformin hydrochloride tablets) therapy, if this is suspected, vitamin B₁₂ deficiency should be excluded.

Drug Interactions:

Glyburide: In a single-dose interaction study in NIDDM subjects, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see DOSAGE AND ADMINISTRATION). Concomitant Glucophage and Oral Sulfonylurea Therapy.

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{1/2} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic Drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUCOPHAGE and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving GLUCOPHAGE, the patient should be closely observed to maintain adequate glycemic control.

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately three times the maximum recommended human daily dose, or a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential

observed with metformin in male rats. However, increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day. No evidence of a mutagenic potential to metformin was found in the Ames test (*S. typhimurium*), genotoxicity test (mouse lymphoma cells), chromosomal aberration (human lymphocytes), or *in-vivo* micronuclei formation (mouse bone marrow).

Fertility of male or female rats was unaffected by administration at doses as high as 600 mg/kg/day, or approximately two times the maximum recommended daily dose on a body surface area basis.

Pregnancy:**Teratogenic effects:**

Pregnancy Category B: Safety in pregnant women has been established. Metformin was not teratogenic in rabbits at doses up to 600 mg/kg/day, or about two times the maximum recommended human daily dose on a body surface area basis. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Animal reproduction studies are not always predictive of human response, any decision to use this drug should be balanced against the benefits and risks.

Because recent information suggests that abnormal glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, there is a consensus among experts that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers:

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in humans, but caution should be exercised in such patients. A decision should be made whether to discontinue the drug, taking into account the benefits and risks of the drug to the mother.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established. Studies in maturity-onset diabetes (MODY) have not been conducted.

Geriatric Use:

Controlled clinical studies of GLUCOPHAGE (metformin hydrochloride tablets) did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other experience has not identified differences in response between the elderly and younger patients. GLUCOPHAGE is known to be substantially excreted by the kidney, so cause the risk of serious adverse reactions, particularly in patients with impaired renal function, greater in patients with impaired renal function, and only be used in patients with normal renal function.

CONTRAINDICATIONS, CLINICAL PHARMACOLOGY, PHARMACOKINETICS:

Because "aging" is associated with reduced renal function, GLUCOPHAGE should be used with caution as age increases. Care should be taken in selection and should be based on careful and frequent monitoring of renal function. Generally, elderly patients should be titrated to the maximum dose of GLUCOPHAGE (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Lactic Acidosis: See WARNINGS, PRECAUTIONS, OVERDOSAGE Sections.

Gastrointestinal Reactions: Gastrointestinal (diarrhea, nausea, vomiting, abdominal bloating, and anorexia) are the most common adverse reactions to GLUCOPHAGE and are approximately 30% in patients on GLUCOPHAGE monotherapy. In treated patients, particularly during initial therapy. These symptoms are transient and resolve spontaneously during continued therapy. Occasionally, temporary dose reduction is useful. In controlled trials, GLUCOPHAGE was discontinued due to gastrointestinal reactions in approximately 1% of patients.

Because gastrointestinal symptoms during therapy appear to be dose-related, they may be relieved by gradual dose escalation and by having patients take GLUCOPHAGE (metformin hydrochloride tablets) (see DOSAGE and ADMINISTRATION). Because significant diarrhea and/or vomiting, dehydration and prerenal azotemia, under certain circumstances, GLUCOPHAGE should be temporarily discontinued.

For patients who have been stabilized on GLUCOPHAGE, nonspecific gastrointestinal symptoms should be attributed to therapy unless intercurrent illness has been excluded.

Special Senses: During initiation of GLUCOPHAGE, approximately 3% of patients may complain of a pleasant or metallic taste, which usually disappears.

Dermatologic Reactions: The incidence of adverse events in controlled clinical trials was comparable for GLUCOPHAGE monotherapy and to sulfonylurea/sulfonylurea therapy.

(See also PRECAUTIONS). During controlled clinical trials of 29 weeks duration, approximately 10% of patients on GLUCOPHAGE monotherapy and 6% of patients on GLUCOPHAGE/sulfonylurea therapy developed symptomatic subnormal serum vitamin B₁₂ levels; serum B₁₂ levels did not decrease significantly. However, only two cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies). An increased incidence of neuropathy has been observed. Therefore, serum B₁₂ levels should be appropriately monitored or periodic parenteral B₁₂ supplementation considered.

DRUG ABUSE AND DEPENDENCE

GLUCOPHAGE possesses no pharmacodynamic properties, either primary or secondary, which could be expected to relate abuse as a recreational drug or addiction.

DOSAGE

Hypoglycemia has not been seen with ingestion of up to 85 mg of GLUCOPHAGE, although lactic acidosis has occurred in such circumstances (see WARNINGS). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

DOSE AND ADMINISTRATION

There is no fixed dosage regimen for the management of hyperglycemia in diabetes mellitus with GLUCOPHAGE or any other pharmacologic agent. Dosage of GLUCOPHAGE should be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose of 2550 mg. GLUCOPHAGE should be given in divided doses with meals and should be started at a low dose, with gradual dose escalation, as described below, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glucose control of the patient.

During treatment initiation and dose titration (see below, INITIAL STARTING DOSE), fasting plasma glucose should be used to determine the therapeutic response to GLUCOPHAGE and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of GLUCOPHAGE either when used as monotherapy or in combination with sulfonylureas.

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, i.e., loss of an adequate glucose lowering response after an initial period of effectiveness.

Periodic reevaluation of GLUCOPHAGE (metformin hydrochloride tablets) may be sufficient during periods of good control in patients usually well-controlled on this drug.

Initial Starting Dose:

Initial starting doses are not seen at doses below 1500 mg per day. However, a lower recommended starting dose and gradually increased dosage is advised to minimize gastrointestinal symptoms.

GLUCOPHAGE 500 mg Tablets:

The usual starting dose of GLUCOPHAGE 500 mg tablets is 500 mg t.i.d. given with the morning and evening meals. Dose increments should be made in increments of one tablet every week, given in divided doses, up to a maximum of 2500 mg per day. GLUCOPHAGE can be administered twice daily (up to 2000 mg per day (e.g., 1000 mg b.i.d. with morning and evening meals). If a 2500 mg daily dose is required, it may be better tolerated given t.i.d. with meals.

GLUCOPHAGE 850 mg Tablets:

The usual starting dose of GLUCOPHAGE 850 mg tablets is 850 mg t.i.d. given with the morning meal. Dose increments should be made in increments of one tablet every week, given in divided doses, up to a maximum of 2500 mg per day. The usual maintenance dose is 850 mg t.i.d. with the morning and evening meals. When necessary, doses may be given 850 mg t.i.d. with meals.

From Other Antidiabetic Therapy:

Transferring patients from standard oral hypoglycemic agents other than chlorpropamide to GLUCOPHAGE, a transition period generally is necessary. While transferring from chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping hypoglycemic effects and possible hypoglycemia.

GLUCOPHAGE and Oral Sulfonylurea Therapy:

If patients have not responded to four weeks of the maximum dose of GLUCOPHAGE monotherapy, consideration should be given to gradual addition of an oral sulfonylurea to continuing GLUCOPHAGE at the maximum dose, particularly if primary or secondary failure to a sulfonylurea

has occurred. Clinical and pharmacokinetic drug-drug interaction-data are currently available only for metformin plus: glyburide (glibenclamide). Published clinical information exists for the use of metformin with either chlorpropamide, tolbutamide or glipizide. No published clinical information exists regarding concomitant use of metformin with acetohexamide or tolazamide.

With concomitant GLUCOPHAGE and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant GLUCOPHAGE and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken. (See Package Insert of the respective sulfonylurea).

If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of GLUCOPHAGE and the maximum dose of an oral sulfonylurea, institution of insulin therapy and discontinuation of these oral agents should be considered.

Specific Patient Populations:

GLUCOPHAGE is not recommended for use in pregnancy or for use in pediatric patients.

The initial and maintenance dosing of GLUCOPHAGE should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOPHAGE.

In debilitated or malnourished patients, the dosing should also be conservative and based on a careful assessment of renal function.

HOW SUPPLIED

GLUCOPHAGE® (brand of metformin hydrochloride tablets) is supplied as white, round, white to off-white, film-coated tablets, available in the following strengths:

500 mg ... Bottles of 100 NDC 0087-6060-05
850 mg ... Bottles of 100 NDC 0087-6070-05

GLUCOPHAGE 500 mg tablets are debossed with BMS 6060 around the periphery of the tablet on one side and 500 across the face of the other side. GLUCOPHAGE 850 mg tablets are debossed with BMS 6070 around the periphery of the tablet on one side and 850 across the face of the other side.

Storage:

Store between 15°-30°C (59°-86°F).

PATIENT INFORMATION ABOUT GLUCOPHAGE® (metformin hydrochloride tablets)

500 mg and 850 mg

WARNING: A small number of people who have taken Glucophage have developed a serious condition called lactic acidosis. Properly functioning kidneys are needed to help prevent lactic acidosis. Most people with kidney problems should not take Glucophage. (See Question Nos. 7-11)

Q1. Why do I need to take GLUCOPHAGE?
 Your doctor has prescribed GLUCOPHAGE (GLUE-co-fahj) to treat your type II diabetes. This is also known as non-insulin-dependent diabetes mellitus (NIDDM).

Q2. What is type II diabetes?

People with diabetes are not able to make enough insulin and/or respond normally to the insulin their body does make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

Q3. How is type II diabetes usually controlled?
 High blood sugar can be lowered by diet and exercise, by a number of oral medications and by insulin injections. Before taking GLUCOPHAGE you should first try to control your diabetes by exercise and weight loss. Even if you are taking GLUCOPHAGE, you should still exercise and follow the diet recommended for your diabetes.

Q4. Does GLUCOPHAGE work differently from other glucose-control medications?

Yes it does. Until GLUCOPHAGE was introduced, all the available oral glucose-control medications were from the same chemical group called sulfonylureas. These drugs lower blood sugar primarily by causing more of the body's own insulin to be released. GLUCOPHAGE (metformin hydrochloride tablets) lowers the amount of sugar in your blood by helping your body respond better to its own insulin. GLUCOPHAGE does not cause your body to produce more insulin. Therefore, GLUCOPHAGE rarely causes hypoglycemia (low blood sugar) and it doesn't usually cause weight gain.

Q5. What happens if my blood sugar is still too high?
 When blood sugar cannot be lowered enough by either GLUCOPHAGE (metformin hydrochloride tablets) or a sulfonylurea

area, the two may. However, if you eat with diet, exercise orally, then your control your diabetes.

Q6. Can GLUCOPHAGE cause side effects?
 GLUCOPHAGE, like many other drugs, can cause side effects. These side effects are minor and rare. Side effects related to GLUCOPHAGE for a while.

Q7. What kind of side effects?
 If side effects occur, they usually go away within weeks in therapy. These side effects include diarrhea, nausea and upset stomach. Taking your GLUCOPHAGE with meals can help reduce these side effects.

Although these side effects are likely to go away, call your doctor if you have severe discomfort or if these effects last for more than a few weeks. Some patients may need to have their dose lowered or stop taking GLUCOPHAGE, either temporarily or permanently. Although these problems occur in up to one-third of patients when they first start taking GLUCOPHAGE, you should tell your doctor if the problem comes back or starts later during the therapy. About three out of one hundred people report having a temporary unpleasant or metallic taste when they start taking GLUCOPHAGE.

Q8. Are there any serious side effects that GLUCOPHAGE can cause?
 GLUCOPHAGE rarely causes serious side effects. The serious side effect that GLUCOPHAGE can cause is called lactic acidosis.

Q9. What is lactic acidosis and can it happen to me?
 Lactic acidosis is caused by a buildup of lactic acid in blood. Lactic acidosis associated with GLUCOPHAGE is rare and has occurred mostly in people whose kidneys are not working normally. Lactic acidosis has been reported about one in 33,000 patients taking GLUCOPHAGE over the course of a year. Although rare, if lactic acidosis occurs, it can be fatal in up to half the cases.

It is also important for your liver to be working normally when you take GLUCOPHAGE. Your liver helps remove lactic acid from your bloodstream.

Your doctor will monitor your diabetes and may periodically test your blood to make sure your kidneys and your liver are functioning normally.

There is no evidence that GLUCOPHAGE causes harm to the kidneys or liver.

Q10. Are there other risk factors for lactic acidosis?
 Your risk of developing lactic acidosis from taking GLUCOPHAGE is very low as long as your kidneys and liver are healthy. However, some factors can increase your risk because they can affect kidney and liver function. You should not take GLUCOPHAGE if:

- You have chronic kidney or liver problems
- You drink alcohol excessively (all the time or short "binge" drinking)
- You are seriously dehydrated (have lost a large amount of body fluids)
- You are going to have certain x-ray procedures with injectable contrast agents
- You are going to have surgery
- You develop a serious condition such as a heart attack, stroke, or a fracture.

Q11. What are the symptoms of lactic acidosis?

Some of the symptoms include: feeling very weak, tired, uncomfortable; unusual muscle pain, trouble breathing, usual or unexpected stomach discomfort, feeling cold, being dizzy or lightheaded, or suddenly developing slow regular heartbeat.

If you notice these symptoms, or if your medical condition has suddenly changed, stop taking GLUCOPHAGE and see your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital.

Q12. What does my doctor need to know to decrease risk of lactic acidosis?

Tell your doctor if you have an illness that results in vomiting, diarrhea and/or fever, or if your intake of fluid is significantly reduced. These situations can lead to dehydration, and it may be necessary to stop taking GLUCOPHAGE temporarily.

You should let your doctor know if you are going to have surgery or specialized x-ray procedures that require injection of contrast agents. GLUCOPHAGE therapy will need to be stopped temporarily in such instances.

Q13. Can I take GLUCOPHAGE with other medications?
 Remind your doctor that you are taking GLUCOPHAGE when any new drug is prescribed or a change is made in how you take a drug already prescribed. GLUCOPHAGE may interfere with the way some drugs work and drugs may interfere with the action of GLUCOPHAGE.

Continued on next page

Glucophage—Cont.**Q14. What if I become pregnant while taking GLUCOPHAGE?**

Tell your doctor if you plan to become pregnant or have become pregnant. As with other oral glucose-control medications, you should not take GLUCOPHAGE during pregnancy.

Usually your doctor will prescribe insulin while you are pregnant. As with all medications, you and your doctor should discuss the use of GLUCOPHAGE if you are nursing a child.

Q15. Are there other risks associated with GLUCOPHAGE?

There is some evidence that any oral diabetes drug may increase the risk of heart problems. Experts are not sure what the real risk for heart problems, if any, from taking oral diabetes medicine.

Q16. How do I take GLUCOPHAGE?

Your doctor will tell you how many GLUCOPHAGE tablets to take and how often. This should also be printed on the label of your prescription. You will probably be started on a low dose of GLUCOPHAGE and your dosage will be increased gradually until your blood sugar is controlled.

Q17. Where can I get more information about GLUCOPHAGE?

This leaflet is a summary of the most important information about GLUCOPHAGE. If you have any questions or problems, you should talk to your doctor or other healthcare provider about type II diabetes as well as GLUCOPHAGE and its side effects. There is also a leaflet (package insert) written for health professionals that your pharmacist can let you read.

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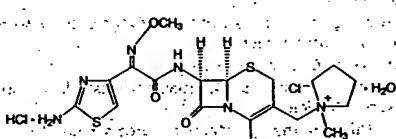
MAXIPIME®

(cefepime hydrochloride) for Injection
For Intravenous or Intramuscular Use

CAUTION: Federal law prohibits dispensing without prescription.

DESCRIPTION

Cefepime hydrochloride is a semi-synthetic, broad spectrum, cephalosporin antibiotic for parenteral administration. The chemical name is 1-[(6R,7R)-7-[2-(2-amino-4-thiazolyl)-glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl[methyl]]-1-methylpyrrolidinium chloride, 7²-({O}-methylxime), monohydrochloride, monohydrate, which corresponds to the following structural formula:



Cefepime hydrochloride is a white to pale yellow powder with a molecular formula of $C_{19}H_{22}ClN_6O_5S_2 \cdot HCl \cdot H_2O$ and a molecular weight of 571.5. It is highly soluble in water. MAXIPIME® (cefepime hydrochloride) for Injection, is supplied for intramuscular or intravenous administration in strengths equivalent to 500 mg, 1 g, and 2 g of cefepime. (See DOSAGE AND ADMINISTRATION.) MAXIPIME is a sterile, dry mixture of cefepime hydrochloride and L-arginine. The L-arginine, at an approximate concentration of .725 mg/g of cefepime, is added to control the pH of the constituted solution at 4.0–6.0. Freshly constituted solutions of MAXIPIME will range in color from colorless to amber.

CLINICAL PHARMACOLOGY**Pharmacokinetics**

The average plasma concentrations of cefepime observed in healthy adult male volunteers ($n = 9$) at various times following single 30-minute infusions (IV) of cefepime 500 mg, 1 g, and 2 g are summarized in Table 1. Elimination of cefepime is principally via renal excretion with an average ($\pm SD$) half-life of $2.0 (\pm 0.3)$ hours and total body clearance of $120.0 (\pm 8.0)$ mL/min in healthy volunteers. Cefepime pharmacokinetics are linear over the range 250 mg to 2 g. There is no evidence of accumulation in healthy adult male volunteers ($n = 7$) receiving clinically relevant doses for a period of 9 days.

Information will be superseded by supplements and subsequent editions

Tissue or Fluid	Dose/Route	# of Patients	Average Concentrations of Cefepime in Specific Body Fluids (µg/mL) or Tissues (µg/g)	
			Average Time of Sample Post-Dose (hr)	Average Concentration
Blister Fluid	2 g IV	6	1.5	81.4 µg/mL
Bronchial Mucosa	2 g IV	20	4.8	24.1 µg/g
Sputum	2 g IV	5	4.0	7.4 µg/mL
Urine	500 mg IV	8	0-4	292 µg/mL
	1 g IV	12	0-4	926 µg/mL
	2 g IV	12	0-4	3120 µg/mL

Absorption

The average plasma concentrations of cefepime and its derived pharmacokinetic parameters after intravenous administration are portrayed in Table 1.

TABLE 1

Average Plasma Concentrations in µg/mL of Cefepime and Derived Pharmacokinetic Parameters ($\pm SD$), Intravenous Administration

	MAXIPIME		
Parameter	500 mg IV	1 g IV	2 g IV
0.5 hr	38.2	78.7	163.1
1.0 hr	21.6	44.5	85.8
2.0 hr	11.6	24.3	44.8
4.0 hr	5.0	10.5	19.2
8.0 hr	1.4	2.4	3.9
12.0 hr	0.2	0.6	1.1
C_{max} , µg/mL	39.1 (3.5)	81.7 (5.1)	163.9 (25.3)
AUC, hr·µg/mL	70.8 (6.7)	148.5 (15.1)	284.8 (30.6)
Number of subjects (male)	9	9	9

Following intramuscular (IM) administration, cefepime is completely absorbed. The average plasma concentrations of cefepime at various times following a single IM injection are summarized in Table 2. The pharmacokinetics of cefepime are linear over the range of 500 mg to 2 g IM and do not vary with respect to treatment duration.

TABLE 2

Average Plasma Concentrations in µg/mL of Cefepime and Derived Pharmacokinetic Parameters ($\pm SD$), Intramuscular Administration

	MAXIPIME (cefepime hydrochloride)		
Parameter	500 mg IM	1 g IM	2 g IM
0.5 hr	8.2	14.8	36.1
1.0 hr	12.5	25.9	49.9
2.0 hr	12.0	26.3	51.3
4.0 hr	6.9	16.0	31.5
8.0 hr	1.9	4.5	8.7
12.0 hr	0.7	1.4	2.3
C_{max} , µg/mL	13.9 (3.4)	29.6 (4.4)	57.5 (9.5)
T_{max} , hr	1.4 (0.9)	1.6 (0.4)	1.5 (0.4)
AUC, hr·µg/mL	60.0 (8.0)	137.0 (11.0)	262.0 (23.0)
Number of subjects (male)	6	6	12

Distribution

The average steady state volume of distribution of cefepime is $18.0 (\pm 2.0)$ L. The serum protein binding of cefepime is approximately 20% and is independent of its concentration in serum.

Cefepime is excreted in human milk. A nursing infant consuming approximately 1000 mL of human milk per day would receive approximately 0.5 mg of cefepime per day. (See PRECAUTIONS, Nursing Mothers.)

Concentrations of cefepime, achieved in specific tissues and body fluids are listed in Table 3. [See table above]

Data suggest that cefepime does cross the blood-brain barrier. The clinical relevance of these data are uncertain at this time.

Metabolism and Excretion

Cefepime is metabolized to N-methylpyrrolidine-N-oxide, which is rapidly converted to the N-oxide (NMP-N-oxide). Urinary recovery of unchanged cefepime accounts for approximately 85% of the administered dose. Approximately 10% of the administered dose is recovered from urine as NMP-N-oxide, as NMP-N-oxide, and 2.5% as an epimer of cefepime. Renal excretion is a significant pathway of elimination; patients with renal dysfunction and patients undergoing hemodialysis require dosage adjustment. (See DOSAGE AND ADMINISTRATION.)

Special Populations

Geriatic patients: Cefepime pharmacokinetics have been investigated in elderly (65 years of age and older) ($n = 12$) and women ($n = 12$) whose creatinine clearance was $74.0 (\pm 15.0)$ mL/min. There appeared to be no difference in cefepime total body clearance as a function of creatinine clearance. Therefore, dosage administration of cefepime in the elderly should be adjusted as appropriate if the patient's creatinine clearance is 60 mL/min or less. (See DOSAGE AND ADMINISTRATION.)

Renal Insufficiency: Cefepime pharmacokinetics have been investigated in patients with various degrees of renal insufficiency ($n = 30$). The average half-life in patients undergoing hemodialysis was $13.5 (\pm 2.7)$ hours and in patients undergoing continuous peritoneal dialysis was $19.0 (\pm 2.7)$ hours. Cefepime total body clearance decreased proportionally with creatinine clearance in patients with abnormal renal function, which serves as the basis for dosage adjustment recommendations in this group of patients. (See DOSAGE AND ADMINISTRATION.)

Hepatic Insufficiency: The pharmacokinetics of cefepime were unaltered in patients with impaired hepatic function who received a single 1 g dose ($n = 11$). (See DOSAGE AND ADMINISTRATION.)

Microbiology
Cefepime is a bactericidal agent that acts by inhibiting bacterial cell wall synthesis. Cefepime has a wide spectrum of *in vitro* activity that encompasses a wide range of gram-positive and gram-negative bacteria. Cefepime has low affinity for chromosomally-encoded beta-lactamase. Cefepime is highly resistant to hydrolysis by β -lactamases and exhibits rapid penetration into most susceptible bacterial cells. Within bacterial cells, the major targets of cefepime are the penicillin binding proteins. Cefepime has been shown to be active against most of the following microorganisms, both *in vitro* and *in vivo*, infections as described in the INDICATIONS AND USAGE section.

Aerobic Gram-Negative Microorganisms
Enterobacter
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Aerobic Gram-Positive Microorganisms
Staphylococcus aureus (methicillin-susceptible only)

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